

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

HERON THERAPEUTICS, INC.,)	
)	C.A. No. 22-985 (WCB)
Plaintiff,)	
)	REDACTED - PUBLIC VERSION
v.)	
)	Original Filing Date: June 22, 2024
FRESENIUS KABI USA, LLC,)	Redacted Filing Date: July 1, 2024
)	
Defendant.)	

HERON THERAPEUTICS, INC.'S OPENING STATEMENT

I. INTRODUCTION

This is a Hatch-Waxman case involving Heron's U.S. Patent Nos. 9,561,229 ("the '229 patent") (JTX-001) and 9,974,794 ("the '794 patent") (JTX-007) (collectively, "patents-in-suit"). The inventions of the patents-in-suit paved the way for the first and only intravenous aprepitant drug product, Heron's CINVANTI®. CINVANTI® is an important drug for treating nausea and vomiting in cancer patients undergoing chemotherapy, the side effects of which can be so debilitating for patients already suffering the hardship of cancer that some would have otherwise stopped their treatment altogether.

The trial in this case has been narrowed to five claims from Heron's two patents: two claims narrowly directed to the formulation (claims 9 and 10 of the '229 patent), one claim directed to the method of treatment using the formulation (claim 21 of the '229 patent), and two claims that include a functional requirement of "physical stability" to the claimed formulation (claims 9 and 10 of the '794 patent).

Infringement: The Court has already ruled that Fresenius's ANDA product infringes claims 9 and 10 of the '229 patent. (D.I. 150 at 18.) Fresenius will be stipulating to infringement

of claim 21 of the '229 patent.¹ At trial, Heron will show by a preponderance of the evidence that Fresenius infringes the remaining two claims.

Heron's expert, Dr. Steven Little, will show that Fresenius's ANDA product meets the three physical stability requirements recited in claims 9 and 10 of the '794 patent as construed. Fresenius does not dispute that its ANDA product has a mean droplet size of not exceeding 500 nm and PFAT5 not exceeding 0.05%, and therefore satisfies the first two physical stability requirements. Fresenius disputes only whether no aprepitant crystals are present in its ANDA product after at least seven days based on 4x to 10x optical microscopy testing. And, notwithstanding the fact that Fresenius represented to the FDA that its product does not have crystals, Fresenius alleges that Heron has failed to prove infringement here because the exact test described in the patent specification was not run. But as Dr. Little will explain, Fresenius performed an even more sensitive test for its ANDA product, which plainly shows that its ANDA product lacks crystals. Fresenius's ANDA product also has the same formulation as CINVANTI®, which is indisputably physically stable. Indeed, Fresenius's expert, Dr. Barrett Rabinow, has admitted that he has "no reason to believe that Fresenius's ANDA product would not be physically stable." (*See* D.I. 150 at 15.)

Obviousness: With no credible infringement defense, Fresenius raises a defense of obviousness, contending that the development of the claimed aprepitant emulsion formulations was routine. Of course, Fresenius bears the burden of proof by clear and convincing evidence, and must not engage in impermissible hindsight. Here, the evidence will show that Fresenius falls well

¹ Fresenius has represented during the June 21, 2024 teleconference with the Court that it will be stipulating that its ANDA product infringes claim 21 of the '229 patent.

short of its burden of proof, and the opinions of its expert, Dr. Rabinow, are tainted with impermissible hindsight.

As Heron's experts will explain at trial, aprepitant had been known for more than 20 years. But in view of aprepitant's extremely low solubility (which has been likened to "cement dust") the development of a formulation that would be appropriate for intravenous ("IV") administration into a patient's bloodstream eluded scientists. These challenges are underscored by the fact that Merck, the company that invented aprepitant and brought it to clinical development, could only succeed in developing an oral formulation. Merck was unable to create an IV formulation of aprepitant. Instead, Merck engaged a team of scientists, including the chemists who created aprepitant, to develop a chemically modified form of the drug, a prodrug referred to as fosaprepitant, in order to get around the difficult physical attributes of aprepitant and bring an IV product to market.

Scientists at Heron were the first to succeed in creating an IV formulation of aprepitant itself, and this formulation is the subject of the patents-in-suit. Heron's patented formulation is an emulsion of aprepitant that uses an unprecedented amount (14%) of a particular excipient, an emulsifier called egg yolk lecithin, in combination with other specific ingredients and concentrations. To date, Heron's product is the only IV formulation of aprepitant approved by the FDA.

Despite this real-world history, Fresenius contends that a person of ordinary skill in the art ("POSA") would have obviously arrived at the claimed invention. According to Fresenius, a POSA would have looked to Chinese Patent Application Publication No. 102379845 ("CN '845") (JTX-071)—which was considered by the Patent Office and never became an issued patent or covered any actual products—and, by cherry picking from this and numerous other references, would have arrived at the claimed invention. In doing so, Fresenius ignores the prior art as a

whole, as *Graham* mandates, and instead starts with the invention and works backwards. Indeed, the evidence at trial will show Fresenius all but ignores the continued published work of the same scientists (Zhou 2012 (JTX-116)) moving *in the opposite direction* from the path that Fresenius says would have been obvious to follow. While CN '845 disclosed amounts of lecithin up to 10%, Zhou 2012 determined the optimized formulation from their research contained 2.5% lecithin, which is far lower than the 14% in Heron's patented invention. (CN '845 (JTX-71.0013); Zhou 2012 (JTX-115.0009).)

Against this backdrop, a POSA facing the problem of developing a new neurokinin-1 ("NK-1") receptor antagonist would have also been confronted with numerous other choices, including selecting active ingredients other than aprepitant (which is one of the claim requirements) and formulation techniques other than an emulsion, which Dr. Rabinow summarily ignores.

Finally, although Fresenius cannot prove a motivation to combine the prior art to make the invention with a reasonable expectation of success, Fresenius also cannot rebut the showing of objective indicia of nonobviousness, including (1) unexpected results, (2) failure of others, (3) long-felt need, (4) commercial success, and (5) copying, which reinforce the hindsight of Fresenius's arguments.

Enablement and Written Description: As an "alternative" to obviousness, Fresenius contends that the asserted patents are invalid for lack of enablement and written description. The legal tests, however, are different. The subject matter available to a POSA is also different (*i.e.*, for Section 112 defenses, the POSA has the benefit of the invention whereas for obviousness the POSA does not). In trying to improperly tie the legal theories together, Fresenius makes self-

contradictory assertions about the state of the prior art, and ignores the teachings of the patent, which are fatal to both its defenses.

II. CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING AND THE DISCOVERY OF CINVANTI®, THE FIRST AND ONLY IV APREPITANT PRODUCT

Chemotherapy-induced nausea and vomiting, otherwise known as “CINV,” is a debilitating side effect of chemotherapy experienced by patients already suffering from cancer. It is one of the most common chemotherapy side effects, and is caused by chemotherapeutic agents that stimulate the peripheral or central pathways of the vomiting centers in the body. It can significantly impact a patient’s quality of life and, in severe cases, lead a patient to quit chemotherapy treatment and succumb to cancer.

Numerous classes of drugs can be used to treat CINV, including NK-1 receptor antagonists—which work by blocking the NK-1 receptor known to be involved in triggering the body’s vomiting center. The first NK-1 receptor antagonist was aprepitant, which was discovered around 1993. (Hargreaves 2011 (JTX-082.0007).) Aprepitant was later approved by the FDA in 2003, and sold as an oral capsule by Merck under the brand name EMEND®. (*Id.*) There was a need, however, for an IV formulation of this class of drugs that could, among other things, minimize patient burden and ensure appropriate delivery of the drug (where patients may be experiencing vomiting). To that end, Merck also worked to develop an IV formulation of its EMEND® product. (Hargreaves 2011 (JTX-082.0005).)

After trying numerous drug development approaches, Merck concluded that the physical and chemical properties of aprepitant precluded its formulation as an IV drug product. (Hargreaves 2011 (JTX-082.0005); MacCoss 2013 (PTX-004.0007-8).) Instead of making an IV aprepitant, Merck designed a new chemical prodrug of aprepitant, fosaprepitant, that had improved water solubility and would convert to aprepitant in the human body. (Hale 2000 (PTX-003.0001);

MacCoss 2013 (PTX-004.0008).) Fosaprepitant, the first IV NK-1 receptor antagonist, was approved by the FDA in 2008 and marketed as EMEND® IV. (EMEND® IV Label (JTX-073.0001).) Although beneficial compared to oral aprepitant, EMEND® IV had its drawbacks, including, for example, infusion-site reactions for certain patients. (Navari 2018 (JTX-139.0011); Leal 2014 (JTX 137.0004).)

The inventors of the patents-in-suit did what Merck scientists and others failed to do: overcame the very low solubility of aprepitant and created a safe and effective IV aprepitant drug product for the treatment of patients suffering from CINV. To do this, the inventors developed a novel emulsion² containing specific ingredients at specific concentrations—including an unusually high amount of egg yolk lecithin as an emulsifier—to achieve a stable IV formulation that permits injection into humans. CINVANTI® is presently Heron’s lead commercial product, with sales revenue of \$484 million from launch in January 2018 through June 2023 funding continued research, development, and the commercial operations of the company.

III. WITNESSES

The Court will hear from the following Heron witnesses who will provide testimony regarding infringement and non-invalidity.

Steven Little, Ph.D.: Dr. Little is the current Chair of the Department of Chemical Engineering and the William Kepler Whiteford Endowed Professor of Chemical Engineering Bioengineering, Pharmaceutical Sciences, Immunology, Ophthalmology at the McGowan Institute for Regenerative Medicine at the University of Pittsburgh. He is an expert in the area of

² An emulsion is a colloidal dispersion of two immiscible liquids in the form of droplets, where droplets of one liquid are dispersed in another liquid in which it is not soluble. Here, CINVANTI® is an “oil-in-water emulsion”.

pharmaceutical science and pharmaceutical formulations, with extensive experience in the development, design, testing, and analysis of formulations.

Dr. Little will provide testimony concerning Fresenius's infringement of the asserted claims. Dr. Little will also respond to Fresenius's invalidity arguments, specifically providing testimony that (1) the asserted claims are not obvious, including testimony regarding objective indicia of nonobviousness, (2) the asserted claims do not lack written description support, and (3) the asserted claims do not lack enablement support.

Jeffrey Hale, Ph.D.: Dr. Hale is a retired chemist from Merck Research Laboratories, who served as a member of the cross-functional team that brought forth EMEND® and EMEND® IV. He is an expert in the area of pharmaceutical science and drug discovery and development, including extensive experience in conceiving of, designing, and developing small molecule drugs.

Dr. Hale will provide an overview of the relevant technology and drug development process as well as testimony concerning objective indicia of nonobviousness, specifically the failure of others and skepticism.

Eric Roeland, M.D., FAAHPM, FASCO: Dr. Roeland is a practicing medical oncologist and palliative care specialist, with experience caring for patients with cancer with poorly controlled symptoms. He is also the Director of Symptom Science at Oregon Health and Science University Knight Cancer Institute, which seeks to improve treatment tolerance and quality of life of patients with symptomatic cancer, including CINV.

Dr. Roeland will provide an overview of the CINV field as well as testimony concerning the long-felt unmet need in clinical practice for an IV NK-1 receptor antagonist used in the care of patients receiving treatment for CINV that was safe (with minimal side effects) and effective.

Mr. Michael Tate: Mr. Tate is an expert in the field of economic analysis, including evaluating commercial success. Mr. Tate will provide testimony concerning the commercial success of CINVANTI®.

IV. FRESENIUS'S ANDA PRODUCT INFRINGES THE ASSERTED CLAIMS

Heron asserts infringement of five claims: claims 9, 10, and 21 of the '229 patent, and claims 9 and 10 of the '794 patent. The Court has already determined that Fresenius infringes claims 9 and 10 of the '229 patent, and Fresenius will be stipulating to infringement of claim 21 of the '229 patent. (*See* D.I. 150 at 18.) The asserted claims are copied below, and the only claim limitation that remains at issue is bolded, underlined, and italicized.

Claim No.	'229 Patent	'794 Patent
Claim 8 (included because claims 9 and 10 depend from claim 8)	An injectable pharmaceutical emulsion comprising: 0.7 wt/wt % aprepitant; 14 wt/wt % egg yolk lecithin; 9 wt/wt % to 10 wt/wt % soybean oil; and a pH modifier, wherein the pH modifier is sodium oleate; wherein the pH of the emulsion ranges from 7.5 to 9.0.	A <i>physically stable</i> pharmaceutical composition suitable for intravenous administration comprising: 0.7 wt/wt % aprepitant; 14 wt/wt % egg yolk lecithin; 9 wt/wt % to 10 wt/wt % soybean oil; and a pH modifier, wherein the pH modifier is sodium oleate; wherein the pH of the composition ranges from 7.5 to 9.0.
Claim 9	The emulsion according to claim 8, wherein the emulsion further comprises 5 wt/wt % sucrose.	The composition according to claim 8, wherein the composition further comprises 5 wt/wt % sucrose.
Claim 10	The emulsion according to claim 8, wherein the emulsion further comprises 2 wt/wt % to 6 wt/wt % ethanol.	The composition according to claim 8, wherein the composition further comprises 2 wt/wt % to 6 wt/wt % ethanol.

Based on the Court's findings, the infringement issue that remains for trial is whether Heron will show that the Fresenius ANDA product would have no aprepitant crystals "present after at least seven days based on 4x to 10x optical microscopy testing." (D.I. 150 at 14.)

The Court construed the term “physically stable” to mean “[m]eets the criteria under USP<729> for mean droplet size not exceeding 500 nm and PFAT5 not exceeding 0.05%, and ***no visible aprepitant crystals when viewed at magnification of 4x to 10x***, after being stored either at 5° Celsius or at room temperature for a period of at least one week.”³ (D.I. 54 at 14-15.) Here, there is no dispute that Fresenius’s ANDA product has a mean droplet size not exceeding 500 nm and PFAT5 not exceeding 0.05%. (Fresenius ANDA 3.2.P.5.1, Specifications (JTX-33.0002); Fresenius ANDA 3.2.P.5.6, Justification of Specifications (JTX-34.0007); Fresenius ANDA 3.2.P.8.3, Stability Data (JTX-35.0002).)

The only remaining dispute with respect to whether Fresenius’s ANDA product is “physically stable” is whether it has no detectable aprepitant crystals from microscopic examination with a 4-10x objective lens at each of the two required temperatures. At trial, Dr. Little will show that Fresenius’s own data utilizing a more sensitive test than that required by the claims demonstrates that Fresenius’s ANDA product had no observable aprepitant crystals in its exhibit batches for at least six months at 25°C ± 2°C and twelve months at 5°C ± 3°C. (Fresenius ANDA 3.2.P.5.1, Specifications (JTX-33.0002); Fresenius ANDA 3.2.P.5.6, Justification of Specifications (JTX-34.0007); Fresenius ANDA 3.2.P.8.3, Stability Data (JTX-35.0002); Method of Analysis (JTX-28.0007).) In addition, the evidence will show that Fresenius designed its ANDA product to be the same as CINVANTI®, and there is no dispute that CINVANTI® had no observable aprepitant crystals based on optical microscopy testing with a 4-10x objective lens. (Heron NDA 3.2.P.5.6, Justification of Specifications (JTX-048.0036-37).) Furthermore, Fresenius’s expert, Dr. Rabinow, has agreed that Fresenius’s ANDA product

³ Unless otherwise indicated, all emphasis has been added, and all internal citations and quotations have been omitted.

contains no crystals when viewed under a magnification of 40x to 100x. Dr. Rabinow also admitted that he has no reason to believe that Fresenius's ANDA Product would not be physically stable after one week. (*See* D.I. 150 at 15.)

**V. FRESENIUS WILL FAIL TO SHOW THAT
THE ASSERTED CLAIMS ARE OBVIOUS**

Fresenius will fall far short of its burden of proving, by clear and convincing evidence, that the asserted claims are obvious. Fresenius's expert, Dr. Rabinow, began his obviousness analysis with the asserted claims and then searched the prior art in an effort to piece together each individual limitation of the asserted claims. In doing so, he centers on a single patent publication, while ignoring the subsequent material work of one of its authors as well as what a POSA would have known about use of emulsifiers in formulations generally. This hindsight-based analysis ignored the prior art as a whole, while also infecting Dr. Rabinow's opinions on motivation to combine various prior art references and whether there would have been a reasonable expectation of success in doing so.

**A. Fresenius's Obviousness Challenge Ignores the
Problem Facing a POSA at the Relevant Time**

As the evidence will show, as of 2014, the challenges in creating an injectable formulation of aprepitant were well known. Aprepitant is not soluble in water and is poorly soluble in oil. These challenging physical properties led Merck, the company that originally discovered the aprepitant compound, to abandon its efforts to formulate an injectable aprepitant product. In the more than 20 years following Merck's discovery of aprepitant, no successful injectable aprepitant formulation was developed. By 2014, the majority of research efforts had shifted to the development of formulations for newer NK-1 receptor antagonists. Indeed, Merck had developed a new compound called fosaprepitant, a prodrug of aprepitant, that was freely soluble in water and was already FDA approved as an intravenous drug product for the treatment of CINV in patients.

Other companies had developed other new NK-1 receptor antagonists that were known to be safe and effective for CINV from phase III FDA clinical trials, including rolapitant and netupitant.

Research into intravenous NK-1 receptor antagonists had expanded to include these new drugs as researchers worked to develop a new intravenous NK-1 receptor antagonist product that had fewer side effects than Merck's fosaprepitant formulation, which was formulated with an excipient that was known to cause side effects in some patients. Dr. Rabinow, however, ignores the available research, and instead focuses narrowly and exclusively on aprepitant emulsions. But as Dr. Little will show, Dr. Rabinow failed to consider all of the choices that would have been available to a POSA at the time of the invention, including NK-1 receptor antagonists other than aprepitant, as well as intravenous formulation techniques other than emulsions. By focusing exclusively on making an aprepitant emulsion, Dr. Rabinow improperly attenuates his obviousness analysis, and fails to show a POSA would have been motivated by the prior art (alone or in combination) to arrive at the inventions of the asserted claims with a reasonable expectation of success.

B. Fresenius's Obviousness Analysis Ignores the Prior Art as a Whole and Focuses on Select Disclosures in CN '845

Dr. Rabinow paradoxically asserts a POSA would have thought that the difficult properties of aprepitant, including water insolubility and poor oil solubility, were an obvious match for an *oil-in-water* emulsion and that they would have had a reasonable expectation of success in developing an aprepitant emulsion through routine experimentation. Dr. Rabinow's arguments not only contradict the scientific literature at the invention date, but Dr. Rabinow's own 2004 review article stating that emulsions were not suitable for compounds that were neither soluble in water nor oil. (Rabinow 2004 (JTX-183.0001-2).)

Dr. Rabinow then goes straight to CN '845 (JTX-071), a Chinese publication of a patent application that is riddled with technical errors and contains no data. To justify his focus on CN '845, Dr. Rabinow will likely suggest that emulsion formulation science fundamentally changed in 2011, and that CN '845 taught that the combination of aprepitant with egg lecithin formed complexes enabling stable emulsions. Yet, CN '845 never even uses the word “complex.” And, Dr. Rabinow even admits that at least one example of CN '845 (Example 6 (0.5 g egg yolk phospholipid)) (JTX-071.0016-17) cannot even form complexes according to his theory because it does not have enough egg lecithin. Multiple other examples in CN '845 do not even use egg lecithin but instead use other emulsifiers with very different properties. (JTX-071.014-17.) Dr. Rabinow ignores these disclosures that are contrary to his assertions, and picks and chooses amongst the many ingredients and concentrations disclosed in CN '845 based on hindsight. And, where CN '845 failed to disclose the claimed ingredient (such as sodium oleate) or the claimed concentration (such as 14% egg lecithin), then—and only then—does Dr. Rabinow look outside CN '845.

Moreover, Dr. Rabinow's approach ignores the subsequent work of the first-listed inventor of the CN '845 publication, Wei Zhou, in the Zhou 2012 publication. (JTX-115.) Zhou described a pre-experimental analysis, from which the authors identified an emulsion recipe containing 0.25% aprepitant, 15% soybean oil, 2 – 4% egg lecithin, 0 – 0.2% oleic acid, 0 – 0.5% poloxamer, and 0 – 3% glycerol. (JTX-115.0007.) The authors continued investigation on the impacts of the egg lecithin, oleic acid, poloxamer, and glycerol concluded that the “optimal formulation of aprepitant emulsions” contained 0.25% aprepitant, 15% soybean oil, 2.5% egg lecithin, and 0.125% oleic acid. (JTX-115.0001.) As illustrated below, this “optimal formulation” shows that

the people who had submitted the CN '845 application took a very different path than the inventors of the patents-in-suit.

Ingredient	Asserted Claims	“Optimized” Zhou Formulation
Aprepitant	0.7 %	0.25 %
Egg yolk lecithin	14 %	2.5 %
Soybean oil	9 – 10 %	15 %
Sodium oleate	as a pH modifier	--
Oleic acid	--	0.125 %
Sucrose	5 % (claim 9)	--
Ethanol	2 – 6 % (claim 10)	--

C. Fresenius Will Fail to Show a POSA Would Have Attempted to Use 14% Lecithin in an Intravenous Formulation (of Aprepitant) Based on the Prior Art

Dr. Rabinow argues that 14% egg lecithin (an emulsifier) would have been obvious to use in an aprepitant emulsion, but, in the entire field of intravenous pharmaceutical emulsions Dr. Rabinow could not find a single emulsion with more than 10% emulsifier.⁴ (*E.g.*, Strickley 2004 (JTX-105.0023) (about 1%), Kamat 2012 (JTX-092.0034) (about 1–5%), Hingorani 2013 (JTX-021.0008) (using 1.2%).) Limiting that collection to emulsions that were actually prepared and evaluated for stability, that number drops to the low single digits. (*Id.*) And the highest amount of emulsifier in either of the two FDA-approved IV pharmaceutical emulsions was 1.2%. (Diprivan Label (JTX-072.0002); Cleviprex Label (JTX-070.0009).) Moreover, Dr. Little will explain how the literature that Dr. Rabinow cited cautioned against higher amounts of emulsifier

⁴ Indeed, the Examiner “did not find a reference that taught aprepitant or any other NK-1 antagonist while also teaching a range encompassing or overlapping 13-15 wt. % emulsifier, much less one teaching 13-15 wt. % egg yolk lecithin” and, with respect to CN '845, found that the “wt % of the egg yolk lecithin is far too low, as is the ratio of egg yolk lecithin to aprepitant.” ('229 patent File History (JTX-002.0162).)

in emulsions because the excess emulsifier can trigger destabilization, including through flocculation (clumping of oil droplets).

Dr. Rabinow will likely rely on the references on microemulsions, including Liu (JTX-093) and Von Corswant (JTX-110), in a veiled attempt to address the fact that none of his cited emulsion literature discloses emulsions that contain anywhere near 14% egg lecithin. This literature, however, is not relevant to emulsions. Microemulsions and emulsions are simply different and not applicable in this context to one another. For example, microemulsions form spontaneously while emulsions require high-energy mixing. Microemulsions are also thermodynamically stable (water and oil phases will not separate over time) while emulsions are thermodynamically unstable. And, microemulsions have very different formulations, which typically includes different emulsifiers (*e.g.*, Solutol HS15) or blends of emulsifiers (*e.g.*, Solutol HS15 and soy lecithin), as well as different oils, and different amounts of oils than emulsions. Dr. Rabinow's reliance on microemulsion literature does nothing to change the fact that he could not find a single prior art emulsion with anywhere near 14% egg lecithin.

Dr. Rabinow will argue that a POSA would have been motivated to increase the amount of emulsifier in an aprepitant emulsion based on his theory of complexation. As with his failure to find a single prior art emulsion with anywhere near the claimed amount of emulsifier, Dr. Rabinow has failed to find a single prior art complexation with anywhere near the claimed ratio of approximately 20:1 (14% lecithin, 0.7% aprepitant). The trio of documents Dr. Rabinow relies on disclose complexes between phospholipids (typically not egg lecithin) and drugs (never aprepitant) in ratios no higher than 3.1:1, and often 1:1. (Bombardelli 1991 (JTX-074), Yue 2010 (JTX-114), Agarwal 2014 (JTX-067).) Additionally, these documents are directed to different drugs and different formulation systems (*e.g.*, aqueous solutions, not intravenous emulsions). (*Id.*) Further,

while Dr. Rabinow will likely rely on Washington (JTX-113) at trial, Dr. Little will explain that this document is inapposite and would not have provided a POSA with any motivation to use anywhere near 14% egg lecithin.

D. Fresenius Will Fail to Show That a POSA Would Have Been Motivated to Use Sodium Oleate in an Intravenous Formulation of Aprepitant

The asserted claims all require sodium oleate as a pH modifier in the emulsion. Neither CN '845 nor Zhou 2012 discloses aprepitant emulsions with sodium oleate. (CN '845 (JTX-071); Zhou 2012 (JTX-115).) As a result, Dr. Rabinow goes outside both of those references to find a disclosure of sodium oleate that he opines will render the claims obvious. But these references would not motivate the use of sodium oleate in an emulsion, including because they either disclose the risk of sodium oleate rupturing blood cells (hemolysis) (Wan 2011 (JTX-112.0035); Jumaa 2000 (JTX-088.0001),) or are not prior art and contain only a passing statement to a use of sodium oleate. (*See* Fell 2015 (DTX-076.0004).) In doing so, Dr. Rabinow again disregards what the driving motivation would be for a POSA: a safe and effective intravenous NK-1 antagonist product with minimal side effects. Dr. Rabinow will not be able to show that a POSA would have selected sodium oleate over other pH modifiers that were more common and had no risks of hemolysis.

E. Fresenius Will Fail to Show That a POSA Would Have Cherry Picked from Selected Disclosures to Arrive at the Claimed Invention

Fresenius's path leading to the claimed invention cherry picks specific excipients and their concentrations from various broad disclosures. Underscoring the hindsight of Fresenius's position, Dr. Rabinow will rely on no fewer than ten references to show that the selection of these excipients in the claimed amounts was obvious. Again, this approach improperly starts with the asserted claims and looks backwards, rather than considering the art as a whole and trying to find a solution to the problem that is facing a POSA.

F. Fresenius Will Fail to Show That a POSA Would Have Had a Reasonable Expectation of Success in Arriving at the Claimed Invention

Finally, Fresenius will be unable to show that a POSA would have had a reasonable expectation of success in combining the disclosures of the prior art to arrive at the claimed invention. At the relevant time, emulsions were rarely used as commercial pharmaceutical products. Moreover, the two FDA-approved IV pharmaceutical emulsion formulations that contained egg yolk lecithin did not use more than 1.2 %, which is a full order of magnitude less than the amount used in the claimed formulation. In addition, neither CN '845 nor Zhou 2012 demonstrate that the formulations they disclose were physically stable, as no stability data on aprepitant crystallization (among other things like PFAT5) is provided. Furthermore, the prior art disclosed significant solubility issues for aprepitant, which would further underscore the lack of a reasonable expectation of success in achieving an intravenous formulation of aprepitant for administration to humans.

G. Examples in the Patents-in-Suit Contradict Fresenius's Assertions That CN '845 and Zhou 2012 Disclosed a Stable Aprepitant Emulsion

The patents-in-suit disclose two experiments in Examples 4 and 5 that show that the prior art aprepitant emulsions were not stable. ('229 patent (JTX-001.0015-16); '794 patent (JTX-007.0015-16).) Example 4 uses the upper bound of the egg lecithin disclosed in CN '845 and it still resulted in aprepitant crystals within four days. Example 5 reproduces the "optimal formulation" disclosed in Zhou 2012 and it also resulted in aprepitant crystals within four days. As neither CN '845 nor Zhou 2012 discloses data on aprepitant crystallization, all available data shows that the prior art formulations were not physically stable, and could not be injected into the arm of a human for treating CINV.

At trial, Fresenius will likely attempt to poke holes in Example 4, but those criticisms are unfounded. Fresenius argues that Example 4 did not follow any specific example from CN '845,

but the evidence will show that the formulation was based on the disclosures in CN '845 in combination with the inventors' efforts to make a formulation with the greatest likelihood of being stable in view of their own internal research. And while Fresenius criticizes Example 4 as having a pH of 7.0, this pH value is squarely in the middle of the disclosed range in CN '845 of pH 6.0 to 8.0. Notably, while Dr. Rabinow attempted to criticize Example 4, he has not raised any specific criticisms for Example 5. Accordingly, there is no genuine dispute that the purportedly "optimal formulation" in Zhou 2012 resulted in aprepitant crystals when tested. Moreover, Fresenius will not be able to show that a POSA would have understood the pH of the Example 5 formulation to differ from that of Zhou. Notably, Fresenius (either itself or through Dr. Rabinow) could have run its own experiments following CN '845 and Zhou 2012 to determine whether the described prior art formulations were, in fact, physically stable, but chose not to do so.

VI. OBJECTIVE INDICIA SUPPORT THE NONOBVIOUSNESS OF THE ASSERTED CLAIMS

Here, the objective evidence provides further support that the claimed invention is not obvious.

Unexpected Results: As described above with respect to Examples 4 and 5, formulations of the prior art were not physically stable and, in fact, resulted in aprepitant crystals within four days. In contrast, the formulation of Example 2, which is an embodiment of the asserted claims, is stable for at 25 °C for three months and at 5 °C for at least ten months. Additionally, CINVANTI® maintained physical stability for at least two years at 5 °C and at least 60 days at 25 °C. This dramatic stability was not expected and has led the way for a safe and effective intravenous aprepitant product that has helped patients treat nausea and vomiting as they undergo chemotherapy.

Failure of Others: The real-world evidence shows that the inventors did what others failed to do—including Merck, which had vast resources and particularized knowledge of the aprepitant compound—in developing an intravenous aprepitant formulation. The first intravenous aprepitant formulation for use in humans was not achieved until the inventors’ unique emulsion formulation, which uses an unusually high amount of egg yolk lecithin to provide unexpected stability to the emulsion.

Long-Felt Need: As Heron’s clinical expert, Dr. Eric Roeland, will explain, the innovative formulation of the claimed invention satisfied a long-felt but unmet need for cancer patients undergoing chemotherapy, a particularly vulnerable patient population. Although EMEND® IV provided a treatment option for patients, its formulation contained the excipient polysorbate 80, which was associated with a high incidence of infusion-site reactions. As a result of these tolerability issues, the Mayo Clinic recommended the use of oral aprepitant over EMEND® IV. A need for a safe and effective intravenous NK-1 receptor antagonist with minimal side effects thus remained, and Heron met this need with the development and commercialization of CINVANTI®.

Commercial Success: As Heron’s economic expert, Mr. Michael Tate, will explain, the commercial embodiment of the asserted claims, CINVANTI®, is a commercial success, and this success is fueled by the innovative formulation of the product. Heron was able to achieve significant sales and market share despite having to overcome competition from EMEND® IV as an earlier entrant into the market and low priced generic fosaprepitant’s market entry in September 2019.

Copying: The nonobviousness of the asserted claims is further demonstrated by the copying of others, including Fresenius. If the prior art formulations of aprepitant were stable and suitable for use in humans, as Dr. Rabinow posits, Fresenius could have copied those formulations

and taken advantage of other abbreviated pathways to bring its product to market (*e.g.*, a 505(b)(2) application). Instead, Fresenius copied the formulation of the patents-in-suit, notwithstanding their listing in the Orange Book for CINVANTI®.

VII. FRESENIUS'S SECTION 112 CHALLENGES FAIL

Fresenius's experts may advance Section 112 arguments that, by their own admissions, are in the alternative to and in contradiction with Fresenius's obviousness arguments. Fresenius has not substantiated any of its 112 arguments. Fresenius's experts have not identified a single inoperative embodiment. Nor have Fresenius's experts identified any reasons why the detailed disclosure of the patents-in-suit, including examples covering the narrowly drawn asserted claims, would not satisfy the written description requirement.

A. The Asserted Method-of-Treatment Claim Is Not Invalid under Section 112

Fresenius may argue that method-of-treatment claim 21 of the '229 is not enabled because a POSA would not be able to recognize the clinical effect of the claimed formulation without undue experimentation, and lacks written description because the specification does not contain any description of preclinical or clinical testing. The evidence will show that this is meritless. In addition to the data contained in the patent specification, including pharmacokinetic data, there is no dispute that aprepitant's clinical effect was well known at the time of the invention and would be achieved by suitable intravenous administration.

B. The Asserted Claims of the '794 Patent Are Not Invalid under Section 112

Fresenius may argue that if the "physical stability" limitation of claims 9 and 10 of the '794 patent is not inherent, then the claims are not enabled and lack written description. Aside from ignoring that inherency cannot supply a motivation to modify or a reasonable expectation of success, Fresenius's argument ignores the realities of formulation science and the teachings of the patents-in-suit. The prior art does not disclose or teach physically stable emulsions of aprepitant,

let alone the claimed inventions. The patent specification, in contrast, provides clear disclosures as to how to make physically stable emulsions meeting the claims of the '794 patent, including exemplary formulations and physical stability testing thereof.

Fresenius also argues that claims 9 and 10 of the '794 patent lack enablement and written description because the claims require a pH within the range of 7.5 – 9.0, and the patent examples test only the pH of 8.74 – 8.92.⁵ The claimed pH range of 7.5 – 9.0 is expressly disclosed in the patent specification, and the inventive examples all use a pH in this claimed range while demonstrating stability over a long period of time. A POSA would understand from the patent specification that the inventors had possession of the disclosed pH range of 7.5 – 9.0, and the invention could be practiced without undue experimentation. Moreover, Fresenius's own ANDA specification allows for a pH range of 7.0 – 8.6, which contradicts its assertions that the claimed pH range is "too broad."

VIII. CONCLUSION

The evidence to be presented at trial will demonstrate beyond a preponderance of the evidence that Fresenius's ANDA product infringes all of the asserted claims. The evidence will further show that the claimed formulation, and its corresponding method of use, represents a significant innovation in the field of drug development. Fresenius's efforts to show that the invention was the obvious outcome of routine work will not hold water. Nor will its efforts to demonstrate invalidity pursuant to Section 112. Fresenius will not be able to satisfy its heavy burden of proving invalidity by clear and convincing evidence.

⁵ To the extent Fresenius seeks to argue that claims 9, 10, and 21 of the '229 are not enabled to their full scope as stable or injectable emulsion (D.I. 157, Exh. 3 at 331-333) on the basis that the claims refers to a "broad range" of pHs, then this argument fails for the same reasons discussed above.

MORRIS, NICHOLS, ARSHT & TUNNELL LLP

/s/ Jeremy A. Tigan

OF COUNSEL:

Bruce M. Wexler
Isaac S. Ashkenazi
Christopher P. Hill
Mark Russell Sperling
Justin T. Fleischacker
Kedar Venkataramani
Stephen Kruse
PAUL HASTINGS LLP
200 Park Avenue
New York, NY 10166
(212) 318-6000

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Jack B. Blumenfeld (#1014)
Jeremy A. Tigan (#5239)
Anthony D. Raucci (#5948)
1201 North Market Street
P.O. Box 1347
Wilmington, DE 19899
(302) 658-9200
jblumenfeld@morrisnichols.com
jtigan@morrisnichols.com
araucci@morrisnichols.com

Attorneys for Plaintiff Heron Therapeutics, Inc.

CERTIFICATE OF SERVICE

I hereby certify that on June 22, 2024, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification of such filing to all registered participants.

I further certify that I caused copies of the foregoing document to be served on June 22, 2024, upon the following in the manner indicated:

Neal C. Belgam, Esquire
Daniel A. Taylor, Esquire
SMITH, KATZENSTEIN & JENKINS LLP
1000 West Street, Suite 1501
Wilmington, DE 19801
Attorneys for Defendant Fresenius Kabi USA, LLC

VIA ELECTRONIC MAIL

Imron T. Aly, Esquire
Kevin M. Nelson, Esquire
Helen H. Ji, Esquire
Julie A. Vernon, Esquire
Mallory McMahon, Esquire
ARENTFOX SCHIFF LLP
233 South Wacker Drive, Suite 7100
Chicago, IL 60606
Attorneys for Defendant Fresenius Kabi USA, LLC

VIA ELECTRONIC MAIL

/s/ Jeremy A. Tigan

Jeremy A. Tigan (#5239)